Postgrad Med J (1990) **66**, 441 - 445

A clinical audit of thallium – technetium subtraction parathyroid scans

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Summary: Eighty six consecutive thallium–technetium subtraction parathyroid scans performed over a three year period for hypercalcaemia have been evaluated. Twelve had chronic renal failure, 11 had hypercalcaemia due to non-hyperparathyroid causes and in 10 the imaging study was technically inadequate. The remaining 53 technically adequate studies performed for hypercalcaemia clinically thought to be possibly due to hyperparathyroidism have been analysed. Of 20 (38%) positive scans, 13 came to surgery (10 correctly localized parathyroid adenomas, 2 with multiple gland hyperplasia, and 1 papillary carcinoma of the thyroid). Of 33 (62%) negative scans, 9 had surgical exploration on the basis of strong clinical grounds and all had parathyroid adenomas.

Multiple biochemical parameters have been assessed in relation to a positive outcome on scan. The adjusted calcium-phosphate product and the ratio of the adjusted calcium-phosphate product to creatinine (Ca × P/Cr) were both significantly lower in the scan positive group ($P < 0.01$). The scan positive group had a significantly higher mean level of PTH ($P < 0.001$) and lower mean level of phosphate ($P < 0.001$).

The present experience shows that parathyroid imaging is useful in localizing parathyroid adenomas in 50% of cases (10 out of 19). This figure is at the lower end of the range of previously published results.

It is less effective in demonstrating multiple gland hyperplasia. The decision as to whether to undertake surgical exploration when the scan is negative has been based successfully on clinical judgement. We feel that an analysis of this nature is important, as it gives insights into the practical relevance of parathyroid imaging in the context of routine clinical work.

Introduction

Hypercalcaemia detected during 'routine biochemical screening' is not uncommon, and in the majority of instances it is due to primary hyperparathyroidism.[1] The role of radionuclide imaging is now established as a useful technique for localizing parathyroid adenomas.[2-4] With increasing access to gamma camera imaging facilities parathyroid scintigraphy is gaining increasing acceptance in the diagnostic work-up of asymptomatic hypercalcaemia. Although several studies have assessed the value of this technique in surgically proven parathyroid adenomas,[3] to our knowledge the outcome of all scans performed in a clinically diagnostic context has not been previously evaluated. The authors feel that such information would be of value in assessing the efficacy of this procedure, as applied in clinical practice and the present study aims to determine this as well as to try and relate a correct outcome on scanning to multiple biochemical parameters.

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Accepted: 6 February 1990

Material and methods

Subjects

Eighty six consecutive subjects who had gamma camera parathyroid imaging performed at the Leicester Royal Infirmary or Leicester General Hospital over the last 3 years were studied. Case notes were analysed to record patient information details, biochemistry, diagnosis, and clinical outcome after the scans. Eleven subjects had hypercalcaemia due to miscellaneous causes; 63 subjects had hypercalcaemia for which there was no obvious cause and clinically thought to be due to primary hyperparathyroidism; 12 had chronic renal failure. Data from subjects with chronic renal failure were not included in the analysis performed as it was felt that these formed a separate group with a distinct biochemical state. Of the 63 suspected primary hyperparathyroidism subjects, there were 53 technically adequate parathyroid scans, and these have been analysed.

Parathyroid imaging technique

With the patient positioned supine, 74 MBq ^{201}Tl (as thallous chloride) was injected intravenously using an intermittent 'butterfly' needle. The butterfly assembly was left *in situ* and kept patent by injecting small amounts of saline as required. Anterior ^{201}Tl images of the neck were acquired between 5–10 minutes and 10–15 minutes after injection using a Siemens ZLC gamma camera and Nodecrest computer. Digital images intended for processing were acquired in zoom mode using a 128 × 128 pixel matrix. Corresponding high resolution (256 × 256) images were simultaneously recorded using the Siemens Scintiview facility. At the completion of the second ^{201}Tl image, 37 MBq Tc99m-pertechnetate was injected through the indwelling butterfly needle. The gamma camera was then tuned for Tc99m. After a further 5 minutes, a static 300 second Tc99m image of the thyroid was acquired.

Before image subtraction, patient movement was checked using the region-of-interest facility on the computer. Minor degrees of movement were corrected using software which 'shifted' a given image horizontally or vertically in one pixel steps. When the images were aligned the 5–10 minutes and 10–15 minutes ^{201}Tl images were summed using standard image processing software. The single Tc99m image was then subtracted from the summed ^{201}Tl image. The optimum degree of subtraction was deemed to have been performed when the resultant count density within the thyroid outline (excluding any 'hot spots') was comparable to the adjacent background.

All images (computer processed images and high resolution unprocessed images) were output on to Kodak 8 × 10 inch NMB film using the Siemens Microdot.

Interpretation was performed by a consultant radiologist with considerable experience in nuclear medicine. All studies were reported blindly, i.e. without knowledge of biochemistry results.[5]

Biochemistry

Routine biochemistry was measured on a SMAC I analyser and serum parathyroid hormone (PTH) was measured using an antibody labelled immunoassay specific for the N-terminal region of the PTH molecule.

Results

Of a total of 53 technically adequate parathyroid scans 20 (38%) were assessed as positive for a parathyroid adenoma, and 33 (62%) were assessed as negative (Table I).

Twenty two subjects came to surgery. Of these, 13 had a positive scan and 9 had a negative scan. Histology showed 19 adenomas (including one ectopic in the mediastinum), two instances of parathyroid hyperplasia, and one papillary carcinoma of the thyroid. Pre-operative parathyroid scanning accurately localized left lower pole adenoma in one out of 4 cases; right lower pole adenoma in 6 out of 7 cases; left upper pole adenoma in one out of 4 cases and right upper pole adenoma in one out of 3 cases (Table II).

Table I Radiological assessment of technically adequate parathyroid scans performed for suspected hyperparathyroidism ($n = 53$)

Positive	20	(38%)
Lower left	3	(5.5%)
Lower right	12	(23%)
Upper left	3	(5.5%)
Upper right	1	(2%)
Ectopic	1	(2%)
Negative	33	(62%)

Association between a positive scan and several direct as well as derived chemical variables was sought. Subjects with a positive scan had lower levels of serum phosphate ($P < 0.001$), when compared to those with negative scans. Significant differences were also observed in the derived chemical variable of phosphate/creatinine ratio ($P < 0.01$), adjusted calcium × phosphate product ($P < 0.01$), and the ratio of the product of adjusted calcium × phosphate to creatinine ratio (Ca × P/Cr; $P < 0.01$) (Table III).

Although subjects with a positive scan had a mean higher level of PTH ($P < 0.001$) (Table III), the N-terminal PTH was not consistently raised in all patients with a proven adenoma, nor was it helpful in predicting a positive or a negative scan (Figure 1).

Of the 11 hypercalcaemia due to non-parathyroid causes, 6 were on thiazide diuretics (4 with negative scans and 2 with equivocal scans); 1 had

Table II Parathyroid scans in relation to surgical exploration

	Surgery	*Positive scan*	*Negative scan*
Total	22	13	9
Left lower	5	2a	3
Right lower	9	8b,c	1
Left upper	4	1	3
Right upper	3	1	2
Ectopic	1	1	0

a: hyperplasia ($n = 1$); b: hyperplasia ($n = 1$); c: papillary carcinoma thyroid ($n = 1$).

Table III Differences between scan-positive and scan-negative groups, mean (s.e.)

	Scan-positive group (n = 20)	*Scan-negative group (n = 33)*	*Statistical significance* P*
Serum PTH	0.99 (0.47)	0.52 (0.06)	<0.001
Serum calcium	2.99 (0.51)	2.90 (0.04)	N.S.
Serum albumin	42.64 (0.59)	42.83 (0.75)	= 0.04
Serum adjusted calcium	2.92 (0.57)	2.83 (0.04)	N.S.
Serum phosphate	0.81 (0.03)	0.88 (0.06)	<0.001
Serum urea	5.84 (0.62)	5.78 (0.50)	N.S.
Serum creatinine	90.64 (8.91)	94.12 (7.55)	N.S.
Serum alk phos	126.12 (14.1)	142.86 (15.9)	N.S.
Serum potassium	4.2 (0.12)	4.2 (0.08)	N.S.
Serum bicarbonate	24.68 (0.62)	25.26 (0.42)	N.S.
Derived chemical variables			
Phosphate/creatinine	0.01 (0.001)	0.011 (0.001)	<0.01
Calcium × phosphate	2.39 (0.08)	2.55 (0.18)	<0.01
Calcium/phosphate	3.87 (0.19)	3.66 (0.25)	= 0.03
(Calcium × phos)/creat	0.029 (0.002)	0.031 (0.003)	<0.01
Calcium/(phos/creat)	339.5 (26.9)	342.8 (30.4)	N.S.
Adj Calcium × phosphate	2.35 (0.07)	2.46 (0.18)	<0.01
Adj Calcium/phosphate	3.76 (0.19)	3.61 (0.25)	= 0.04
(Adj Calcium × phos)/creat	0.029 (0.002)	0.031 (0.003)	<0.01
Adj Calcium/(phos/creat)	334.2 (29.8)	316.2 (24.0)	N.S.
Adj Calcium × PTH(phos/creat)	177.7 (34.8)	467.9 (38.7)	<0.001

*Student's *t* test; N.S.- not significant; phos - phosphate; creat - creatine; adj - adjusted; PTH - parathyroid hormone.

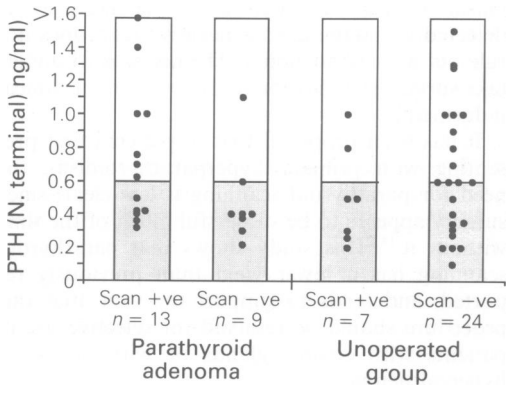

Figure 1 Thallium–technetium scans in proven and presumed primary hyperparathyroidism. (▨ , Reference range <0.6 ng/ml).

carcinoma of the colon (negative scan); 2 had multiple myeloma (both negative scans) and 2 had spurious hypercalcaemia (both negative scans).

Discussion

Previous studies of radionuclide parathyroid imaging have examined the value of the procedure in selected groups of patients with biochemically proven hyperparathyroidism who were destined for surgery, or followed up specifically because of their presence in a clinical trial.[3,4,6,7] The test has a reported accuracy of approximately 80% in localizing parathyroid adenomas preoperatively. In the present study, of 19 surgically proven adenomas, the preoperative parathyroid scan accurately localized 10 (50%). This lower accuracy may be due to the fact that this study was designed to assess the value of the test in the general 'work-up' of patients with hypercalcaemia, that is in patients with no identifiable cause (such as myeloma, chronic renal failure, secondary deposits, sarcoidosis, thyrotoxicosis), and therefore suspected of having primary hyperparathyroidism. Another noteworthy feature of the study is that only 13 of the 20 positive scans actually came to surgery. The decision whether or not to proceed to surgical exploration was based on the judgement of the attending clinician and as such may give a truer reflection of what may be expected in routine clinical practice.

In each of two patients with four gland hyperplasia, the subtraction image showed a single 'hot spot'. It is notoriously difficult to pick up overactivity in all the glands in hyperplasia.[8]

Part of the reason for this failure may be due to the small size of some hyperplastic glands, or it may be that the uptake of thallium in hyperplastic glands is functionally different to adenomas.

Nine patients with a negative scan had a surgically proven adenoma. Parathyroid imaging is known to be limited by its lack of sensitivity in localizing adenomas less than 0.5 g[9,10] and these may make up almost one third of all adenomas excised.[4] There were 13 patients in the unoperated group with a raised PTH level but with negative scans, and it is not clear as to the extent the results of the parathyroid scan may have influenced the decision as to whether or not to operate.

As might be expected, a significant difference was observed in serum PTH between the scan-positive and scan-negative groups. PTH assay may not always be immediately accessible. The authors have attempted, therefore, to determine whether a positive scan may be associated with any of the routinely measured biochemical parameters. Subjects in the scan-positive group had a significantly lower serum phosphate, adjusted calcium-phosphate product and Ca × P/Cr. In the present study all patients with a proven parathyroid adenoma had a Ca × P/Cr below 0.03. Further work is suggested to determine whether a particular level of such a derived biochemical variable can consistently be related either to a positive scan or parathyroid adenoma. If this were the case then this might be used as an inexpensive screening procedure before proceeding to parathyroid scanning, especially as these estimations are now routinely included in serum multiautomated analysis.

The present study differs from previously published studies in that it represents an analysis of parathyroid scans from the point of unselected clinical practice. Most patients were referred in the hope that parathyroid imaging would 'provide a diagnosis' for the observed hypercalcaemia, and this again is reflected in the low overall positive rate of such scans. A higher yield may be expected if parathyroid imaging is reserved for 'localization' of an adenoma when the clinical and biochemical features strongly suggest primary hyperparathyroidism. It is also of interest that a wide scatter of levels for PTH was seen in the present study, and that there was no apparent 'cut off' point for predicting with confidence, the outcome of parathyroid imaging. One possible explanation may lie in the relative insensitivity of the N-terminal assay, and the limitations of this. Up to 38% of patients with primary hyperparathyroidism may be misclassified by this.[11] In the present study only 24 out of 53 patients had an abnormally raised PTH level (Figure 1), and this may account for some degree of confusion resulting in patients proceeding to parathyroid scanning unnecessarily. More sophisticated PTH assays should help to resolve this problem.

Two patients with apparent hypercalcaemia (raised total serum calcium, but normal albumin adjusted calcium) were erroneously investigated along the lines of hyperparathyroidism. Not surprisingly they had normal PTH levels and scans.

Albumin adjusted total serum calcium is well recognized as a more sensitive index of calcium homeostasis rather than total calcium.[12] This should be assessed and interpreted correctly before undertaking further expensive investigations.

With the widespread use of multiautomated serum analysis, the biochemical features of mild primary hyperparathyroidism may present to a variety of clinical disciplines. Controversy exists as to whether the management of this should be by conservative means or by surgical intervention.[13] In the present study there were 2 patients with a positive scan and raised PTH, and 5 with a positive scan but normal PTH (Figure 1) who did not come to surgery. This decision would appear to have been taken on clinical grounds. We would suggest that parathyroid scans should be undertaken only when surgical intervention is considered necessary in the mangement of the patient, and should serve as an adjunct to surgery.

Our experience of gamma camera parathyroid imaging over a three year period would suggest that this technique is useful in localizing parathyroid adenomas in 50% of unselected cases. It is less effective in demonstrating multiple gland hyperplasia. Larger adenomas are more likely to be detected by imaging, so a negative scan does not rule out a small adenoma. The decision to undertake surgical exploration must be based on clinical judgement.

It has been proposed that in patients first presenting with primary hyperparathyroidism, the need for parathyroid scanning is less clear, since surgery appears to be successful much of the time without it.[14] This study shows that parathyroid scanning has a lower yield than previously reported, and tends to support the view that this procedure should be reserved for selective use in patients with ectopic glands or with persistent hypercalcaemia.[15,16]

Acknowledgement

We are grateful to the departments of Medicine, Surgery, Pathology, Nephrology and Medical Records at the Leicester Royal Infirmary and Leicester General Hospital for their help during this study, to the several consultants in various disciplines who have allowed us to use data on patients under their care, to the SAS Laboratories, University Hospital of Wales, Cardiff for PTH assay; and to Ms Judy Noble for her secretarial assistance.

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